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EDITORIAL COMMENT

Reverse Left Ventricular Remodeling After Kidney Transplantation

Unraveling the Complex Autointoxication of Uremia*

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"Uremia is a complex auto-intoxication, the variegated clinical picture being the summation of the effects of retention of various urinary constituents."
— Dr. Arthur Maurice Fishberg, in *Hypertension and Nephritis*, 1940 (1)

Uremia has long been recognized to disrupt the normal physiology of numerous organs, including the heart (2,3). Over the last 30 years, echocardiography studies have found adverse changes in cardiac structure and function associated with end-stage renal disease (ESRD), which is collectively termed uremic cardiomyopathy. These cardiac abnormalities, including left ventricular hypertrophy and systolic dysfunction, are common in hemodialysis and are associated with an increased risk of adverse clinical outcomes (4). However, the precise nature of the uremic mediators of cardiac dysfunction remain elusive. Kidney transplantation is the treatment of choice for selected patients with ESRD. A successful kidney transplantation improves the quality of life and reduces the mortality risk for most patients compared with maintenance dialysis (5). However, 50% to 60% of deaths among kidney transplantation recipients are directly attributable to cardiovascular disease. In addition, death from cardiovascular disease is also the most common cause of graft loss, accounting for 30% of graft loss from death overall (6). Thus, severe ischemic cardiomyopathy (ejection fraction [EF] <30%) is a relative contraindication to kidney transplantation.

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In this issue of the *Journal*, Hawwa et al. (7) report the results of an observational study that describes the effects of successful kidney transplantation on cardiac structure and function and predictors of post-transplantation survival. They retrospectively examined a cohort of 232 patients with echocardiography studies available for analysis before and after kidney transplantation (7). They found that left ventricular ejection fraction (LVEF) significantly increased for the whole cohort (53% to 56%; $p = 0.002$), with a greater magnitude of increase in the 66 patients with pre-transplantation left ventricular systolic dysfunction (LVSD) (41% to 50%; $p < 0.001$). In the group with pre-transplantation LVSD, the improvement in EF was accompanied by other significant changes consistent with reverse remodeling, including reduced LV end-diastolic dimension, reduced LV mass, reduced LV wall thickness, and reduced estimated right ventricular systolic pressure. Although pre-transplantation LVEF was significantly associated with increased risk of post-transplantation mortality, in the 32 patients with a post-transplantation increase in EF of ≥10%, survival was not significantly different from that of patients with normal pre-transplantation systolic function. Hawwa et al. (7) also found several clinical variables that were associated with regression of LV mass post-transplantation, including body mass index, change in systolic and diastolic blood pressures, and change in hemoglobin levels. However, only the increase in hemoglobin levels and estimated glomerular

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filtration rate (2 clinical measures associated with better allograft function) were significantly associated with an increase in LVEF. In addition, the rise in hemoglobin was an independent predictor of post-transplantation survival.

The observed improvement in LVEF after kidney transplantation is consistent with previous studies with serial measurements of cardiac function in kidney transplantation populations (8), previous studies that investigated the effects of more intense dialysis on cardiac function (9,10), and experimental results that have consistently demonstrated the cardiotoxic effects of uremic serum in single cell preparations, isolated papillary muscles, and the intact heart (11–14). The cohort used by Hawwa et al. (7) was larger than that used in previous reports and included older subjects, who were more often treated with current guideline-recommended therapies for LVSD both before and after transplantation. Interpretation of the findings was limited by the observational study design in a cohort selected on the basis of available echocardiographic results obtained a median of 422 days after transplantation. This design also introduced immortal time bias because only fitter patients who survived for 12 to 18 months to undergo post-transplantation echocardiography were included in the study. The retrospective observational study design did not allow inference of a causal relationship among the reported associations. Nonetheless, when taken together with previous related studies (8), the results of this study suggest that ESRD patients with LVSD should not be routinely excluded from consideration for kidney transplantation. Additional investigation is needed to identify clinically useful predictors of post-transplantation reverse remodeling and outcomes in dialysis patients with systolic heart failure.

A novel finding of the current study is that the post-transplantation change in hemoglobin levels was significantly associated with a post-transplantation change in LVEF, and was also independently associated with post-transplantation survival after adjustment for EF. In previous reports with smaller populations, an increase in hemoglobin (and reversal of other metabolic derangements associated with the uremic state) after kidney transplantation was not significantly associated with a change in LVEF. The observed association between a change in hemoglobin and survival is consistent with a large body of literature that has demonstrated a comparable relationship in non-dialysis patients with chronic heart failure (15). A causal association between a change in hemoglobin and survival seems unlikely, because previous randomized trials have failed to demonstrate survival benefit of treatment with erythropoietic agents in anemic patients with heart failure and chronic kidney disease (16–18). Iron deficiency is unlikely a contributory factor, because intravenous iron supplementation is routinely administered to promote erythropoiesis in anemic dialysis populations. Accordingly, the observed association is likely attributable to other unmeasured nutritional, metabolic, and clinical factors associated with the uremic state that affect both cardiac function and effective erythropoiesis (19). Hemodilution related to pre-transplantation systolic heart failure could also contribute to the findings, because the observed difference in the hemoglobin change is driven primarily by the lower pre-transplantation hemoglobin in these patients (20). It is also possible that the reported association is a spurious finding related to the bias inherent in the selection of the cohort.

In conclusion, the current study provides an important contribution to the existing literature linking improved renal function after successful kidney transplantation to improved cardiac structure and function. Additional investigation to characterize the nature of the "complex autointoxication" associated with uremia might reveal novel therapeutic targets to affect reverse LV remodeling, potentially improving survival in patients with systolic heart failure and concomitant chronic kidney disease.

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